REMARKS

I. Interview with the Examiner

Applicants and their agent are appreciative of the Interview that took place on August 10, 2004 as summarized by the Interview Summary of record.

II. Petition for Extension of Time

Applicants herewith petition the Commissioner for Patents to extend the time for response to the Office Action mailed April 7, 2004 for three months from July 7, 2004 to October 7, 2004. Authorization is given to charge the extension of time fee of $475.00 (37 C.F.R. §§1.136 and 1.17) to Deposit Account No. 23-1703. Any deficiency or overpayment should be charged or credited to the above numbered deposit account.

III. Restriction Requirement of Record

The restriction requirement of record includes the following elected embodiments:

- medical device – stent
- matrix – fullerene
- antibody attachment – covalent
- vessel type – artery
- matrix attachment – covalent.

In the event that the amended independent claims are found to define an allowable genus, the Examiner is respectfully requested to withdraw the restriction requirement and to rejoin the withdrawn claims and/or embodiments for examination in the present application.

IV. Amendments to the Specification and Claims

The Abstract has been amended by the removal of any seemingly legal phraseology and to be more concise in satisfaction of the 150 word maximum. Removal of the objection to the specification is requested.

By this Amendment, claims 3, 28 and 56-61 have been cancelled and new claims 62-76 have been added. Claims 6, 10-17, 19, 26, 33-37, 40, 42, 46, 48 and 51-55 remain withdrawn from consideration as being drawn to a non-elected species. The claims to be considered for further examination on the merits are 1, 2, 4, 5, 7-9, 18, 20-25, 27, 29-32, 38, 39, 41, 45 and 62-76.

In general, the claims have been amended to more clearly define the claimed invention. For example, claim 1 has been amended to recite transitional expressions where appropriate. Specifically, amended claim 1 recites that the medical device is coated with a composition comprising one or more antibodies and one or more layers of a matrix. The one or more antibodies is selected from the group consisting of antibodies, fragments thereof and combinations of the antibodies and fragments which react with an endothelial cell surface antigen. Support is provided by the definition and discussion of the term antibodies at pages 13-15 of the specification.

Amended claim 1 does not recite a specific matrix material, e.g., a fullerene. The recitation of possible matrix materials has been relegated to dependent claim status (See claims 20, 63, 70 and 74). Furthermore, claim 20 has been amended to recite that the matrix can also comprise a mixture of the materials included in the Markush group. Support is provided by original claim 10 having the open-ended expression "comprising" to define the matrix of the claimed invention.

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Independent claims 18, 25, 29 and 38 were amended in a similar manner as claim 1. Claim 38 was also amended as suggested by the Examiner by the deletion of the word "a" before -- medical device --.

Claims 56-61 have been cancelled and, therefore, the objection to claims 56-57 and the rejection of claims 56-61 under 35 U.S.C. §112, second paragraph, are moot.

Applicants submit that no new matter has been introduced by any of the amendments to the specification and/or claims.

V. Claim Rejections – Dekker et al.

In this Section V, Applicants will discuss the obviousness rejections under 35 U.S.C. §103(a) of medical device claims 1, 2, 4, 5, 7-9, 38 and 39 and method of treatment claims 29-32 (¶¶9-11 and 14 of the Office Action). The §103 rejection of each of these claims is based on the same combination of primary and secondary references. In certain instances, a tertiary reference is cited. Nevertheless, it would seem expedient for both the Examiner and Applicants to simultaneously address the §103 rejections of the medical device and method of treatment claims.

The primary reference is Dekker A. et al, *Thrombosis and Haemostasis*, "Improved Adhesion and Proliferation of Human Endothelial Cells on Polyethylene Precoated with Monoclonal Antibodies Directed against Cell Membrane Antigens and Extracellular Matrix Proteins", F.K. Schattauer Verlagsgesellschaft mbH (Stuttgart) 66(6) 715-724 (1991) ("Dekker"). The secondary reference is US 5,310,669 to Richmond et al. ("Richmond").

As stated in the Interview Summary, Applicants discussed the differences between claim 1 and Dekker. The following is a restatement of that discussion.

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a. The claimed invention

The claimed invention is directed to a coated medical device which, after insertion into an artery or vein, captures *in vivo* circulating cells by the reaction between (1) antibodies bound to the surface of the coated medical device and (2) endothelial cell surface antigens. Once captured and attached to the surface of the device, the cells undergo cellular development and proliferate (See page 10, lines 1-7 and Example 2).

The claimed medical device provides an immunoaffinity surface characterized by a high selectivity for detecting and capturing cells circulating in the bloodstream, e.g., progenitor cells, which after capture, attach to and proliferate on the surface of the coated stent. Advantageously, there is a decrease and/or reduction of restenosis and thrombosis when the immunoaffinity surface of the medical device is coated with the body's own cells.

In summary, therefore, it is possible with the claimed invention to achieve *in vivo* detection, selection, capture and proliferation of circulating cells on the surface of the claimed medical device that is layered with at least one or more antibodies and one or more layers of a matrix. The one or more antibodies is selected from the group consisting of antibodies, fragments thereof and combinations of the antibodies and fragments which react with an endothelial cell surface antigen.

b. The primary reference – Dekker

A close inspection of Dekker shows that the primary reference makes a distinction between adhesion of endothelial cells to the substrate and proliferation of endothelial cells on the substrate.

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The data in Dekker at pages 717-718 and Figure 3 show that adherence of endothelial cells is obtained when monoclonal antibodies CLB-HEC 19 and CLB-HEC-3477, both of which are stated on page 716 of Dekker to be antibodies to membrane (glyco)protein of human endothelial cells, are coated on the surface of a synthetic vascular graft. However, when endothelial cell proliferation is considered, Dekker states that these same two antibodies did not support proliferation (See, pages 718-719 and Figures 5-6). This is further emphasized in Dekker at page 722 in the right-hand column where it is stated that proliferation of endothelial cells is probably dependent on deposition of extracellular matrix proteins, i.e., fibronectin and von Willebrand factor, which are known to be adhesive proteins (See page 721).

Therefore, one distinction between the claimed invention and Dekker is the failure of Dekker to disclose or suggest proliferation of circulating cells on a polyethylene layer with surface–adsorbed monoclonal antibodies directed against endothelial cell membrane proteins. In contrast, the claimed invention shows not only adhesion but also proliferation of captured cells when the claimed medical device is coated with the same class of antibodies.

There is yet another important difference between the claimed invention and Dekker. The disclosure of Dekker is limited to the *in vitro* coverage of vascular grafts with ***seeded endothelial cells***. This disclosure is in striking contrast to the claimed invention which achieves *in vivo* selection and adhesion of ***cells circulating in the bloodstream*** and, after capture, proliferation of the cells on the surface of the medical device.

In summary, therefore, Dekker discloses that attachment of seeded endothelial cells is achieved with a surface coating of monoclonal antibodies directed against endothelial cell-specific membrane antigens. However, proliferation did not occur on these surface-adsorbed antibodies. Rather, as stated at the end of the summary, Dekker reports that attachment and

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proliferation require two categories of monoclonal antibodies: (1) antibodies directed against plasma membrane antigens of human endothelial cells and (2) antibodies directed against the adhesive proteins von Willebrand factor and fibronectin. In contrast to Dekker, the claimed coated device and coating composition advantageously provide a surface coated with only one class of antibodies which captures circulating cells which then become attached to the surface and proliferate to form a surface that decreases and/or prevents restenosis and thrombosis.

c. Secondary and tertiary references

Claims 1-2, 4, 7, 9, 38 and 39 are rejected under 35 U.S.C. §103(a) as being unpatentable over Dekker in view of US 5,310,669 to Richmond ("Richmond"). The secondary reference to Richmond is cited by the Examiner for the alleged disclosure of a substrate surface coated with a fullerene matrix for attaching and growing cells. Richmond is similar to Dekker in that the disclosure of Richmond is limited to the attachment and growth of ***seeded cells*** in an ***in vitro*** environment, e.g., a cell culture substrate. There is no disclosure or suggestion by Richmond of inserting a coated medical device into an artery or vein to select and capture circulating cells onto the coated surface of the medical device on which captured cells proliferate and develop. Therefore, Richmond cannot overcome the deficiencies of Dekker.

Claim 5 is rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Dekker, Richmond and US 5,688,486 to Watson et al. ("Watson"). Claim 8 is rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Dekker, Richmond and in view Asahara et al., Science 275: 964-967 (1997) ("Asahara"). Claims 29-32 are rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Dekker, Richmond and Bos et al., Archives Phsio. Biochem 106; 100115 (1998) ("Bos").

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For all of the foregoing reasons, Applicants respectfully submit that a *prima facie case of obviousness* has not been established. Dekker does not disclose or suggest the claimed invention. None of the secondary or tertiary references overcome the failure of Dekker to suggest the claimed invention. Withdrawal of the §103 rejection of medical device claims 1, 2, 4, 5, 7-9, 38 and 39 and method of treatment claims 29-32 is requested.

VI. Claim Rejections – Richmond

This Section VI discusses the obviousness rejection under 35 U.S.C. §103(a) of composition claims 18, 20-24 and 56-61 and method of coating claims 25 and 27 (¶¶12 and 13 of the Office Action). These claims are directed to a composition and method for coating a medical device with the composition comprising a matrix and a therapeutically effective amount of at least one type of antibody that reacts with an endothelial cell surface antigen. With respect to the §103 rejection of the composition claims, the Examiner again relies on Dekker and Richmond. However, in this case, the primary reference is Richmond and the secondary reference is Dekker.

Claims 56-61 have been canceled. Independent claims 18 and 25 have been amended to clarify that the claimed coating composition and coating method render a medical device compatible for *in vivo* attachment and proliferation of cells on the surface of the coated medical device. As discussed in Section V, above, the respective disclosure of Richmond and Dekker is limited to the *in vitro* seeding of coated or uncoated surfaces with endothelial cells. Furthermore, as noted by the Examiner, Richmond is silent with respect "to the antibody reacting with an endothelial cell antigen and the substrate being a medical device" (Office Action at page 7). Thus, the Examiner relies on Dekker as the secondary reference.

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However, Dekker admits the inability to achieve cell proliferation with the composition and method of claims 18 and 25, respectively. Similarly, the tertiary reference to Asahara does not disclose or suggest *in vivo* proliferation. A stated in the abstract, Asahara discloses the isolation of putative endothelial progenitor cells from human peripheral blood and *in vitro* differentiation of these cells.

For all of the foregoing reasons, Applicants submit that none of the cited references, whether taken alone or in combination, suggests a coating composition or method that render a medical device compatible for *in vivo* attachment and proliferation of cells on the surface of the coated device. As such, a *prima facie* case of obviousness based on the combination of Richmond and Dekker has not been established with respect to claims 18, 20-22, 24, 25 and 27. The tertiary reference to Asahara does not overcome the failure of Richmond and Dekker to suggest the claimed invention and, therefore, a *prima facie* case of obviousness with respect to claim 23 has not been established. Withdrawal of the §103 rejection of composition claims 18, 20-25 and 27 is requested.

In the event that the obviousness rejection of the claimed composition is maintained, Applicants submit that the claimed coating method, i.e., claim 25, is nevertheless patentable since, in such case, the claimed coating method must be deemed to represent a new use of an old composition.

VII. Double Patenting

Claims 1, 18, 25, 27, 29-31, 38, 39, 56, 58, 60 and 61 are provisionally rejected under the judicially created doctrine of obviousness type double patenting as allegedly being unpatentable over claims 10, 27, 32, 33, 35, 37, 42, 45 47 and 49 of co-pending U.S. Patent Application Serial

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No. 10/360,567. The Examiner alleges that the conflicting claims, although not identical, are not patentably distinct from each other. It is further alleged that the claims of the current application include all of the limitations of the co-pending application and are broader.

Since the rejection is provisional, Applicants will respond to the rejection at such time that the claims of either application have been patented.

VIII. Allowable Subject Matter

Applicants are appreciative of the allowance of claims 41 and 45. Claims 3 and 28 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 3 and 28 have been re-written as new claims 65 and 72, respectively. For all of the preceding reason, Applicants submit that the claimed invention as defined by all of the pending claims is patentable. Therefore, at this time, it is respectfully submitted that there is no reason to limit a patent for the claimed invention to the embodiments of claims 3, 28, 41 and 45.

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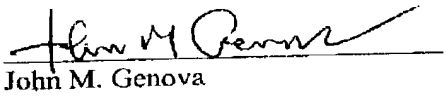
CONCLUSION

Applicants have made a good faith attempt to respond to the Office Action. Claims 1, 2, 4, 5, 7-9, 18, 20-25, 27, 29-32, 38, 39, 41, 45 and 62-76 are directed to patentable subject matter. Accordingly, Applicants request reconsideration and allowance of the claims.

Any additional fee due in connection with this communication should be charged to Deposit Account No. 23-1703.

Dated: September 27, 2004

Respectfully submitted,



John M. Genova
Reg. No. 32,224
Attorney for Applicants

Customer No. 07470
Attorney Direct Dial: (212) 819-8832

Attachment: Abstract

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ABSTRACT

A medical device coated with one or more antibodies and one or more layers of a matrix is disclosed. The antibodies or fragments thereof react with an endothelial cell surface antigen. Also disclosed are compositions and methods for producing the medical device. The matrix coating the medical device may be composed of a synthetic material, such as a fullerene, or a naturally occurring material. The fullerenes range from about C60 to about C100. The medical device may be a stent or a synthetic graft. The antibodies promote the adherence of cells captured *in vivo* on the medical device. The antibodies may be mixed with the matrix or covalently tethered through a linker molecule to the matrix. Following adherence to the medical device, the cells differentiate and proliferate on the medical device. The antibodies may be different types of monoclonal antibodies. By facilitating adherence of cells to the surface of the medical device, the disclosed methods and compositions will decrease the incidence of restenosis as well as other thromboembolic complications resulting from implantation of medical devices.

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